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"Shifted" Threshold May Explain Diversity of Cardiovascular Malformations in Multiple Congenital Abnormalities Syndromes: 3C (Ritscher-Schinzel) Syndrome as an Example

Iosif W. Lurie and Charlotte Ferencz

Department of Epidemiology and Preventive Medicine, School of Medicine, University of Maryland at Baltimore, Baltimore

The *analysis* of cardiovascular malformations (CVM) in 3C (Ritscher-Schinzel) syndrome showed at least 9 types of CVM in 24 cases, including 4 cases from the Baltimore-Washington Infant Study. The proportion of different CVM forms was similar to that of the general population. The same is also true for many other syndromes of multiple congenital abnormalities (MCA), due either to aneuploidy or to Mendelian mutation. Such a wide spectrum of very different CVM in patients with the same entity has yet to be explained. According to the hypothesis proposed, the basic mutation (or chromosome imbalance) affects cellular homeostasis and leads to the "shifting" of a threshold to the left. This allows the expression of some genes silent under normal conditions. The principle of the shifted threshold is applicable to the explanation of the origin of many other defects in MCA syndromes.

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INTRODUCTION

Cardiovascular malformations (CVM) are important findings in hundreds of Mendelian syndromes of multiple congenital abnormalities (MCA) [Burn, 1987]. CVM are also frequent manifestations in virtually all forms of autosomal aneuploidy. In most cases with a Mendelian syndrome there is no single form of CVM, but a wide diversity of CVM types occurs in patients with the same syndrome. For example, CVM are found in approximately ⅔ of patients with Fryns syndrome, but among 29 patients who had CVM many different forms of heart defects were reported. The ratio between various CVM types in Fryns syndrome was approximately the same as among all newborn infants with CVM [Ferencz et al., 1993]. The same phenomenon is typical also of patients with Meckel, Roberts, "pseudotrisomy 13", von Voss-Cherstvoy, all forms of "short rib—polydactyly," and many other MCA syndromes.

CVM is one of the basic manifestations in the newly-recognized 3C (cranio-cerebello-cardiac) syndrome [Ritscher et al., 1987]. The variety of CVM in this syndrome was studied recently by Digilio et al. [1995]. Four cases of 3C syndrome found in the Baltimore-Washington Infant Study (BWIS) prompted us to reanalyze this spectrum. We also try to explain how one mutation may lead to very different forms of cardiac defects.

METHODS AND RESULTS

The BWIS is a regional case-control study of CVM in liveborn infants during 1981–1989 [Ferencz et al., 1993]. According to the BWIS, among 4,390 infants with CVM, 1,116 (~25%) had additional extracardiac defects. "Nonchromosomal" syndromes and associations were found in 246 cases, and 3C (Ritscher-Schinzel) syndrome was diagnosed in 4 of these cases (Table I). These data do not allow an estimate of the incidence of 3C syndrome among newborn infants, as some patients do not have CHD [Marles et al., 1995], and in some cases with CVM, cerebellar defects (another basic diagnostic finding) may be lacking. However, it is evident that at least among patients with CVM, 3C syndrome takes on a significant role.

Our observations brought the total number of reported cases of Ritscher-Schinzel syndrome with CVM up to 24 (Table II). In this group, different forms of

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Address reprint requests to Iosif W. Lurie, M.D., Department of Epidemiology and Preventive Medicine, University of Maryland at Baltimore, 660 W. Redwood St., Rm. 132, Baltimore, MD 21201-1703.

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TABLE I. Descriptive Information on BWIS Cases With 3C Syndrome*

BWIS no.	1777	3553	10082	10576
Sex	Female	Male	Female	Female
Race	White	White	Black	White
Birth weight (kg)	1.41 (33 weeks)	4.14	3.03	3.27
Survival	Alive at 1 year	Alive at 1 year	Died at 1 year	Died at 6 days
Maternal age	20 years	34 years	32 years	28 years
Paternal age	24 years	24 years	41 years	41 years
Pregnancy order	1	3	8	3
Outcome of other pregnancies	Trisomy 21 in a girl (2nd pregnancy)	1 nl child, 1 child with Marfan syndrome and mitral valve prolapse	3 nl children from other men, 1 spontaneous and 3 induced abortions	2 girls and twin-brother of proband are normal
Type of CVM	Membranous VSD (operated), ASD (spontaneously closed)	Small VSD, abnl mitral valve, dilated aortic arch[a]	Membranous VSD	HLH
Brain defects	Dandy-Walker malformation	Dandy-Walker malformation	Dandy-Walker malformation	Dandy-Walker malformation
Other defects	Hypertelorism, inguinal hernia	Hypertelorism, cleft lip and palate, cleft larynx, excess nuchal skin, hypospadias	Plagiocephaly, hypopituitarism	"Facial dysmorphism," excess of nuchal skin
Comments		Father died of Marfan syndrome		

* abnl, abnormal; nl, normal; VSD, ventricular septal defect; ASD, atrial septal defect; HLH; hypoplastic left heart.
[a] Manifestation of Marfan syndrome (patient had both 3C and Marfan syndrome).

CVM were found; 10 patients had ventricular septal defects (VSD), including one with supracristal VSD, 5 had endocardial cushion defects, and in some cases tetralogy of Fallot, double-outlet right ventricle, hypoplastic left heart, atrial septal defects, and pulmonic and aortic stenoses were also reported. This distribution is similar to the population distribution of different forms of isolated CVM in newborns.

DISCUSSION

This phenomenon might be explained in several ways. First, some morphologic forms of CVM may actually be only different steps of the same morphogenetic defect. As cyclopia and cebocephaly are not separate entities, but different manifestations of the same basic pathology (holoprosencephaly), certain variants of CVM may be only various manifestations of the same basic defects of cardiogenesis. But the very wide spectrum of CVM forms makes this explanation unlikely, at least in this particular case.

Most isolated CVM are considered to be determined by polygenic inheritance [Burn, 1987]. This does not exclude specific Mendelian genes responsible for certain stages of cardiogenesis, and responsible (when mutated) for some specific cardiac defects (as is evident, for example, in Holt-Oram or Noonan syndromes). Nevertheless, the contribution of Mendelian forms in the total pool of CVM is relatively small. In all other cases, definite CVM will occur only if a concentration of abnormal genes is above the threshold. In some MCA syndromes, primary defects resulting from a mutation may affect the very basic processes of cellular homeostasis, and therefore may lead to *shifting of a threshold to the left*. As a result, individuals who are homozygous for such mutations may develop CVM due to the their own "weak" genes, although their concentration is far below threshold for normal conditions. In such a case, the primary mutation may not even be directly related to cardiogenesis itself, but may act mainly by its own "weak" genes and allowing them to be expressed.

Because normally most individuals have a subthreshold concentration of mutant genes involved in cardiogenesis, the spectrum of CVM in such a syndrome will be wide and similar to the distribution of these forms among patients with isolated CVM. The uneven sex distribution among patients with 3C syndrome and CVM (18 girls and only 4 boys) speaks in favor of a "polygenic" explanation.

Actually, this principle may be important not only for CVM, but also for other "polygenic" malformations (cleft lip and palate, pyloric stenosis, hip dislocation, etc.). In each embryo, specific susceptibility to a particular multifactorial/threshold trait will determine which malformations (in any) will be manifested in that embryo.

Basically, the same hypothesis is applicable also for most defects in patients with chromosome abnormalities. A wide spectrum of CVM is observed in almost any chromosomal syndrome. Certainly, as for single-gene mutations, it does not contradict the possibility of specific effects due to the excess or deficiency of particular chromosomal segments, as is obvious in distal 8p dele-

TABLE II. Cardiovascular Defects in Patients With 3C Syndrome*

Authors	Sex	Type of CVM
1. Yarom and Fried, 1971	F	Aortic stenosis, pulmonic stenosis
2. Ritscher et al., 1987	F	AVSD
3. Ritscher et al., 1987	F	AVSD
4. Mims and Say, 1989	F	Tetralogy of Fallot
5. Verloes et al., 1989	F	Supracistal VSD
6. Gurrieri and Neri, 1992	M	VSD with parachute mitral valve
7. Iglesias et al., 1993	?	VSD, ASD, patent ductus arteriosus
8. Iglesias et al., 1993	F	VSD
9. Quintana et al., 1994	F	DORV, pulmonic stenosis
10. Hoo et al., 1994	F	AVSD
11. Hoo et al., 1994	F	Pulmonic stenosis, ASD
12. Wörle et al., 1994	F	VSD
13. Digilio et al., 1995	F	AVSD, tetralogy of Fallot
14. Marazzo and Mulvihill, 1995	F	Tetralogy of Fallot
15. Marles et al., 1995	F	VSD
16. Marles et al., 1995	F	DORV
17. Marles et al., 1995	F	AVSD
18. Marles et al., 1995	F	DORV
19. Marles et al., 1995	M	VSD
20. Marles et al., 1995	M	Tetralogy of Fallot
21. BWIS #1777	F	VSD, ASD
22. BWIS #3553	M	VSD, abnormal mitral valve, dilated aortic arch
23. BWIS #10082	F	VSD
24. BWIS #10576	F	Hypoplastic left heart

* AVSD, atrioventricular septal defect; VSD, ventricular septal defect; ASD, atrial septal defect; DORV, double-outlet right ventricle.

tions and trisomy 21 (atrioventricular septal defects), distal 11q deletions (hypoplastic left heart), or dup(8q)/del(8p) (outflow tract defects). But most CVM in cases of chromosomal pathology may be related to a significant shift of the threshold to the left. The same principle might be useful in explaining numerous examples of cleft lip and palate, pyloric stenosis, postaxial polydactyly, etc., in syndromes where these defects are not characteristic.

Generally, "chromosomal" syndromes involve more serious changes in homeostasis. Therefore, most likely, chromosome abnormalities will lead to the shifting of thresholds to the left in different polygenic systems (although shifts to the right cannot be excluded). As a result, a high incidence of many "polygenic" defects (which are not characteristic findings of the syndrome) could be explained in this way. For example, although occurrence of cleft palate in 4 out of 47 patients with distal 9p deletion (but no associated imbalance) significantly exceeds its incidence in the newborn population, most likely this abnormality is a result of the changed threshold. If this is true, the search for specific genes leading to such common defects (but uncommon for the given entity) in chromosomal syndromes is bound to fail.

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